Drug Discovery and Development for Reward Disorders: Views from Government

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INTRODUCTION AND CONTEXTUAL ISSUES

The National Institute on Drug Abuse (NIDA) is the world’s largest research institution dedicated to funding research on drugs of abuse, prevention of drug abuse, and treatment of substance abuse disorders. Being an institution of the US Federal Government, NIDA derives its existence and objectives from Congressional and legislative activities. NIDA was created by the Drug Abuse Office and Treatment Act of 1972 (PL 92-255). This act stipulated that NIDA be established within the National Institute on Mental Health and become operational in 1974, at which time NIDA became one of three institutes in the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). NIDA started to receive large funding increases in 1986; funding for acquired immune deficiency syndrome (AIDS) research was especially increased. The Anti-Drug Abuse Act of 1988 (PL 100-690) further increased NIDA funding; $8 million was appropriated for medication development projects. With this Congressional impetus and funding, NIDA began its Medications Development Program. Congressional intent was for NIDA to develop pharmacotherapies to treat the symptoms and disease of drug abuse,

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including medications to: block the effects of abused drugs; reduce craving for abused drugs; moderate/eliminate withdrawal symptoms; block or reverse toxic effects of abused drugs; and prevent relapse in detoxified persons. The organizational structure of NIDA was restructured in 1990 to create the Medications Development Division, now called the Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMC). In 1992, The ADAMHA Reorganization Act (PL 102-321) transferred NIDA to the National Institutes of Health (NIH). This act also stipulated that the NIDA Medications Development Program should pursue biological and pharmacological approaches to develop medications for treatment of heroin and cocaine addiction; establish a close working relationships with the pharmaceutical industry; conduct studies to gain approval of new medicines for addiction treatment; and develop a working relationship with Food and Drug Administration (FDA) to assure that efficacy of compounds is expeditiously evaluated and approved.

The Anti-Drug Abuse Act of 1988, which initiated funding for the NIDA Medications Development Program, was a tacit acknowledgement that the pharmaceutical industry needed incentives to consider medications development in the area of addictive disorders. Congress, in the ADAMHA Reorganization Act of 1992, further stipulated that the Federal Government should contract with the National Academy of Sciences (NAS) to establish a committee of the Institute of Medicine (IOM) to review issues impacting the development of medications for addiction. An IOM committee was convened in 1993. This committee examined the extent to which the limitations of the (then) current scientific knowledge hindered the development of pharmacological treatments, reviewed the progress of the NIDA Medications Development Program, considered the role of the FDA and other government entities in the addiction medications approval process, surveyed the incentives and disincentives to private sector development of medications to treat addictive disorders, and attempted to determine the (then) current role of the private sector in such development.

To gain a better understanding of how industry viewed medications development for addictive disorders, the IOM committee sent a survey to pharmaceutical companies. Nineteen companies responded. Although a myriad of issues were discussed, the state of the science, the stigma associated with medications for treatment of addiction, the difficulty of performing clinical studies in substance abusing patients, and reimbursement issues were noted to be of concern to companies (Appendix D, The Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector, 1995).

DIVISION OF PHARMACOTHERAPIES AND MEDICAL CONSEQUENCES OF DRUG ABUSE

Drug Discovery Program – Initial Operations

The DPMC initiated a discovery and development program in 1990. The initial program intended to perform standardized tests and clinical studies to facilitate the discovery and development of addiction medications and to facilitate the involvement of the pharmaceutical industry and academia. Setting up a medications discovery
program within a company is an expensive undertaking. Moreover, many companies lack the scientific expertise in the neurobiology of drugs of abuse and behavioral pharmacology of addiction. The NIDA discovery program was shaped with the consultation of outside advisors who were members of the (then) Pharmaceutical Manufacturers Association. The primary objective of this discovery program was to discover putative medications for the treatment of cocaine dependence. Smaller discovery teams were also set up to discover medications for opiate, and later (after 2000) methamphetamine and nicotine dependence. Only the cocaine discovery program will be discussed here. To set up the discovery program and ensure its success, four separate tasks had to be initiated. The first task was to set up an appropriate testing hierarchy, using both *in vitro* and *in vivo* assays. Based on past successes in developing medications for other drug addiction disorders, the initial testing scheme of the NIDA Cocaine Treatment Discovery Program was focused on the discovery of “cocaine agonist therapies” (analogous to methadone for heroin addiction or nicotine replacement therapy for smoking) and “cocaine antagonist therapies” (analogous to naltrexone for heroin addiction). Behavioral tests, comprising locomotor activity, drug discrimination, and self-administration in rodents, formed the first tier of animal testing. These tests were selected as a trio because advisors from both academia and the pharmaceutical industry did not feel that any one of these tests had predictive validity. Drug discrimination and self-administration in monkeys formed the second tier of behavioral testing. The dopamine transporter was featured as a primary target, but it was acknowledged from both a scientific and programmatic standpoint that cocaine interacted with other monoamine transporters and, indirectly, with several different types of biogenic amine receptors. In evaluating potential “cocaine agonist therapies,” including compounds targeting the dopamine transporter, the ideal candidate compound was considered to be one that produced less maximum effect than cocaine (especially with regard to stimulation of locomotor activity), with a slow onset and long duration of action. As the science and the program have progressed over the last 17 years, the molecular targets have become more diversified and testing procedures have evolved (see below).

The second task was to determine how to obtain compounds for testing and to establish appropriate policies for compound and data handling. Compounds were purchased from chemical catalogs and obtained from Government chemists, NIDA grantees, and the pharmaceutical industry. Pharmacological testing was to be performed “free of charge,” NIDA testing sites were to be blinded to the identity and source of compounds, and the results were to be sent to compound submitters and kept confidential by NIDA. The “licensing” component of the NIDA discovery program differs from that of industry in that NIDA does not pay companies or chemists to “license” compounds. Instead, compound submitters retain their full intellectual property rights. The reliance on compounds from outside sources is another deviation from the usual way that industry works. Most companies that have in-house discovery programs have full control of the discovery process whereas NIDA must rely on collaborating entities for compound supply and re-supply. This arrangement can hamper the pace of discovery.

The third task was to determine the type of agreements that would be used to obtain compounds for testing. The NIH Office of Technology Transfer has developed several documents that can be used for the transfer of materials to and from NIH laboratories or its contractors. Information about a compound or compound series
may be transmitted after a Confidential Disclosure Agreement has been executed. Depending on the intellectual property status of a compound and the concerns of the compound submitter, a compound may be obtained under a Material Transfer Agreement, a Material Cooperative Research and Development Agreement (MCRADA) or a Screening Agreement. The Screening Agreement is a custom document written by NIDA that allows compounds to be tested without concern that NIDA or its contractors will patent a compound that has gone through preclinical testing. In order for NIDA to offer such protection, a Declaration of Exceptional Circumstances (DEC) had to be obtained from the US Commerce Department for each contract that supports compound testing. The default position of the Federal Government is that contractors own data generated under their contracts and can file invention reports and patents. The DEC rescinds the default position of the Government, disallowing specified contractors from owning data and patenting. As mentioned above, NIDA testing sites are blinded to the identity and source of compounds; this helps NIDA to control the use of data and ensures that NIDA can abide by its agreements with compound submitters. In addition, the contractors are legally required to treat as confidential any and all compound-related data or other information, whether provided by NIDA or generated during the course of testing.

The fourth task was the development of a decision algorithm for compounds to progress through preclinical development. A detailed discussion of DPMC clinical trial capabilities is beyond the scope of the present chapter; however, taking the ability of NIDA to conduct clinical trials for granted, a discovery program is of no use if promising compounds cannot advance to clinical testing. To facilitate preclinical development, NIDA established contracts to support standard toxicological and pharmacokinetic testing, as well as specialized safety studies. Each post-discovery/early development compound, termed a Safety Assessment Candidate (SAC), undergoes limited toxicological and pharmacokinetic testing to determine whether advancement to full, Investigational New Drug (IND)-enabling development is warranted. For compounds advancing beyond SAC status, special drug interaction studies are conducted to evaluate the safety of potential medications in the presence of drugs of abuse. The need for these special drug interaction studies follows from the fact that many patients will ultimately use drugs of abuse on top of any medication that is prescribed for the treatment of drug addiction. Because patients often abuse multiple drugs, a battery of drug interaction studies is required; for example, all new molecular entities (NMEs) under development as cocaine addiction treatments are evaluated for safety in the presence of cocaine, an opiate (morphine), and ethanol.

**Drug Discovery Program – Current Status**

To date, over 3000 compounds have been evaluated in the NIDA drug discovery programs. Three compounds have been advanced to IND status and two more are being developed for administration to human subjects. The IND for the first of these should be filed in early 2008.

The structure, objectives, and testing scheme of the NIDA drug discovery programs have changed as a result of the maturing of the science and efforts to improve efficiency. Medication targets have expanded and relapse prevention has become the
number one focus. In 2005, the Addiction Treatment Discovery Program (ATDP) was created through the merger of four separate discovery programs that were focused exclusively on cocaine, opiates, methamphetamine, and nicotine. As mentioned above, a major goal of the earlier programs was the discovery of “agonist therapies” to facilitate quit attempts in cocaine and methamphetamine dependence. In contrast, the ATDP has shifted focus to emphasize the discovery of compounds aimed at the clinical endpoint of relapse prevention. Because of the focus on relapse prevention as a clinical endpoint, the program has a number of drug self-administration reinstatement procedures (relapse models) using different drugs of abuse. The ATDP has increased resources to evaluate compounds in models of relapse to cocaine, heroin, or methamphetamine, using stress, conditioned cues, or drug primes to produce reinstatement in rats whose self-administration behavior has been extinguished.

ATDP staff coordinates testing for compound submitters and provide related study reports and feedback. In addition to the relapse models mentioned above, established tests that could be selected for a particular compound include in vitro receptor assays, rodent locomotor activity and intra-cranial self-stimulation testing, rodent and/or primate drug discrimination testing, and rodent and/or primate drug self-administration testing. In addition, a series of predictive toxicology tests – such as the hERG channel assay to predict QT prolongation and the Spot Ames test to predict mutagenicity – are available and, as necessary, additional animal models may be used. Compound testing is shaped by existing data in rodents and the sequence of testing is determined in collaboration with the compound submitter. ATDP staff members welcome opportunities to discuss specific testing proposals with potential compound submitters and to present NIDA’s capabilities to pharmaceutical company management.

Development of Medications for Opiate and Cocaine Addiction

The motivation for Federal involvement in the development of medications for the treatment of addictive disorders is from a public health viewpoint. This is one obvious difference between NIDA and the pharmaceutical industry. The Federal Government is heavily invested in the treatment of addictive disorders and views new medications to treat these disorders as a way to expand treatment and improve the public health of the United States.

Another major difference between the NIDA Medications Development Program and the pharmaceutical industry is the aspect of commercialization. From a legal

1 Please refer to Heidbreder, Impulse and reward deficit disorders: Drug discovery and development; Koob, The role of animal models in reward deficit disorders: Views of academia; Markou et al., Contribution of animal models and preclinical human studies to medication development for nicotine dependence; and Rocha et al., Development of medications for heroin and cocaine addiction and regulatory aspects of abuse liability testing, in this volume for further description and discussion of animal models of substance abuse and relapse, and procedures used to evaluate the efficacy of compounds to treat reward deficit disorders.
standpoint, the US Government does not compete with its citizens or private commercial enterprises. OMB Circular A-76 establishes Federal policy regarding the performance of commercial activities and implements the statutory requirements of the Federal Activities Inventory Reform Act of 1998, PL 105-270. Suffice it to say that the NIH has interpreted this to mean that they expect its pharmaceutical partners to market any commercial products that are the realization of joint research between NIH and its partner(s). NIDA does not wish to undertake the full medications development process on its own. Therefore, NIDA seeks to enter into collaborative agreements with private sector partners as early as possible in any development project. As collaborative agreements are established, the relative contributions of each party are negotiated on a case-by-case basis and a formal agreement is drafted. NIDA has a Technology Transfer section that negotiates the necessary legal agreements under which joint projects are conducted.

One of the initial challenges for the NIDA Medications Development Program was to demonstrate to the pharmaceutical industry that its grantees and contractors could perform clinical trials that would pass muster at the FDA. This was a two-part challenge: the initial challenge was to design appropriate clinical trial endpoints and the second component was to execute the trial according to Good Clinical Practices guidelines. When the program was just beginning in the early 1990s, there were three potential development candidates for the treatment of opiate dependence. Each will be discussed in turn.

Levomethadyl acetate, or LAAM, had been studied in the 1970s and had two previous New Drug Applications (NDAs) rejected by the FDA. Following a consultation with the FDA, it was agreed that a large (26 site) multi-center trial would be run. Six hundred and twenty-three subjects were recruited in about 1 year. Subjects were allowed to stay on LAAM for 65 weeks. NIDA worked with a contractor, Biometric Research Institute, to file a successful NDA. LAAM was approved for marketing 18 days after the NDA was filed.

Buprenorphine was the second of the three development candidates. Following the successful demonstration of the efficacy of buprenorphine to reduce opiate use in the outpatient setting by NIDA Intramural Research Program, NIDA signed a CRADA with Reckitt-Colman (now Reckitt-Benckiser) to develop buprenorphine as a medication for the management of opiate dependence. A subsequent multi-center trial, run by one of NIDA’s grantees, showed dose-related efficacy. During the development process it became apparent that a solid dosage form needed to be developed. Although this was a challenge, it also presented an opportunity to add naloxone (a narcotic receptor antagonist) to prevent abuse by intravenous injection. The buprenorphine to naloxone ratio was decided after reviewing data from three clinical pharmacology studies that were subsequently published. A subsequent multi-center trial of the buprenorphine and buprenorphine/naloxone 4:1 ratio combination was compared to placebo responses in the first month of opiate therapy. Both buprenorphine dosage forms outperformed placebo in reducing opiate use in the outpatients setting. These data and other developed by NIDA grantees and contractors were used successfully to obtain NDA approvals for buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) in October 2002. These are the first two opiates in 90 years
that can be prescribed by qualified physicians in office-based settings for the management of opiate dependence. Over 10 000 physicians have qualified, either by training or experience, to prescribe buprenorphine. Reckitt-Benckiser estimates that over 500 000 patients have been prescribed buprenorphine for the management of opiate dependence.

The last development candidate, a depot naltrexone formulation, was initially developed by a NIDA contractor. Subsequently, the contract operation was purchased by Alkermes, who decided to market the depot naltrexone (Vivitrol®) for the treatment of alcohol dependence. Clinical studies with other NIDA-supported depot naltrexone dosage forms have shown efficacy in the treatment of opiate dependence. Although this last study may be regarded as a proof of concept trial, it demonstrates that NIDA and its grantees can successfully perform clinical trials with different dosage forms in this difficult to treat population.

NIDA has tried to address industry concerns by demonstrating the feasibility of performing high-quality, large-scale clinical trials in substance abusing populations, demonstrating that it has developed outcome variables and statistical analyses that are scientifically valid and accepted by FDA as capable of demonstrating efficacy for a drug product, and shown its ability to partner with industry for successful development of drug products. This last point implicitly suggests that NIDA has knowledge of the developmental pathways for successful medications research and development for addictive disorders. The ongoing success of the buprenorphine products is a further demonstration that markets exist where others were skeptical of any degrees of successful marketing of a medication for addiction.

The NIDA Medications Development Program is acutely aware of the need for medications for the management of stimulant addictions. NIDA grantees and contractors have tested over 60 marketed psychopharmaceuticals in cocaine-dependent patients. Several of these medications have shown salutary effects to reduce cocaine use (for a comprehensive review see 8) and are undergoing confirmatory clinical trials. None of the medications to date, for example, disulfiram, has shown a large effect size. NIDA grantees and contractors are also testing several marketed medications for the treatment of methamphetamine dependence. Recently, two medications, methylphenidate and bupropion, have shown preliminary efficacy in amphetamine-dependent 9 and methamphetamine-dependent subjects, 10 respectively.

There are three challenges that NIDA must meet in order to develop effective medications for stimulant dependence. The first is to continue to conduct confirmatory clinical trials. Medications that demonstrate efficacy in these studies will be the first generation of medications for the treatment of stimulant dependence. The second is to evaluate and develop medications that have a neuroscience-driven basis. Recent examples of mechanisms of interest include cannabinoid receptor antagonists 11 and D3 dopamine receptor antagonists. 12,13 Testing of the neuroscience-based medications will also give some indication of the importance of modulating appetitive behaviors in the treatment of addictive disorders. The third challenge is to use feedback and feedforward mechanisms to discover the relevant animal and human laboratory models that have predictive validity.
ANIMAL MODELS IN THE DISCOVERY OF DRUG ADDICTION TREATMENTS

The Validity of Animal Models in the Field of Drug Addiction

In the field of medications discovery for drug addiction treatment, it is fortunate to have animal models that meet many criteria for validity. The fact that alcoholism can only follow the consumption of alcohol or that cocaine addiction can only follow exposure to cocaine is often taken for granted; however, the importance of such knowledge to the “etiological validity” of the animal models should not be overlooked. One can administer the causative agents of drug addiction (the drugs themselves) to animals to produce the disorder under study. Contrast this situation with that of researches who long for similar etiological validity in animal models of psychosis or dementia. Beyond etiological validity, animal models that involve ethanol drinking or lever-pressing to receive intravenous injections of a drug such as cocaine show exemplary face validity. Likewise, the similar symptomatology of opiate withdrawal in monkeys and man is a noteworthy example of construct validity. Finally, preclinical studies of the two most recently approved drug addiction treatment medications, varenicline and buprenorphine, demonstrate the predictive validity of drug self-administration procedures as models of nicotine and opiate addiction, respectively.

Despite the generally high level of validity seen in animal models of addiction, it must be acknowledged that predictive validity has not been established for animal models relevant to the field’s most important clinical indications, those for which no effective medications are currently available. Clearly, if there is no medication with well-established efficacy in treating a specific drug addiction disorder (e.g., in the case of cocaine or methamphetamine addiction), there can be no relevant animal model with established predictive validity. The same can be said for novel approaches to drug addiction treatment. For example, an animal model of stress-induced relapse to opiate abuse cannot be appropriately evaluated for its predictive validity if clinical studies have not revealed a medication that effectively prevents stress-induced relapse to opiates. Where predictive validity cannot be established, we must rely on the etiological, construct and/or face validity of our animal models.

Use of Data from Animal Models for “Go/No Go” Decisions

Because it is not possible to obtain data from animal models with established predictive validity when focusing on clinical indications that lack effective medications (the tools for validation), it is fortunate that the FDA does not have a firm requirement for such data. In fact, advancement to clinical development does not necessarily require efficacy-related preclinical data. Preclinical safety data are always required but the case

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Please refer to Koob, The role of animal models in reward deficit disorders: Views of academia; in this volume; Large et al., Developing therapeutics for bipolar disorder (BPD): From animal models to the clinic; Steckler et al., Developing novel anxiolytics: Improving preclinical detection and clinical assessment in Volume 1, Psychiatric Disorders; Wagner et al. Huntington Disease, in Volume 2, Neurologic Disorders for further discussion regarding concepts of validity in animal models of behavioral disorders.
for potential efficacy in the clinic can be based on a strong theoretical rationale. If it is determined that the potential benefits outweigh the potential risks, then clinical concept testing may progress without supportive preclinical efficacy data.

If preclinical efficacy data are not essential for advancement to clinical development, then why bother with animal models? How one answers this question depends on projected costs of advancing to clinical trials, available resources, and the willingness to take risks. Advancement of a novel compound into development is always a gamble. It costs millions of dollars to shepherd a single NME through preclinical and Phase I safety testing and, unfortunately, the large majority of NMEs must be dropped before advancement to clinical efficacy trials; unexpected toxicities and/or undesirable pharmacokinetic properties are the most common reasons for failure. Including the cost of failures, average out-of-pocket costs for each successful NDA approval have been estimated at $403 million (in 2000 US dollars) within the pharmaceutical industry. Research and development are no less expensive and the odds of success are no greater within the Government. Given cost considerations, it is not surprising that management usually requires preclinical data suggestive of efficacy before compounds are advanced to development. Thus, while FDA reviewers may not require preclinical efficacy data for their “go/no go” decisions, the financial burden of drug development makes such data important for the drug developer’s “go/no go” decision process. Advancing an NME to development is regarded as less risky in the presence of promising data from animal models, even if the predictive validity of the models is unknown.

A compelling case for initiating a development project in the absence of promising preclinical efficacy data can be made when animal models are lacking (this does not appear to be the case in the field of drug addiction) or when few costs would be incurred beyond those associated with the clinical efficacy trial. The latter situation occurs when a compound that is marketed for one indication (e.g., Parkinson’s disease, depression, or attention deficit hyperactivity disorder) is considered for evaluation in another (e.g., cocaine or methamphetamine addiction). Within NIDA, we also see this situation when a pharmaceutical company has made the initial investment to advance a compound through preclinical and clinical safety testing and the compound has failed for its primary indication. In fact, the most common reason for a company to initiate contact with NIDA regarding a potential collaboration is the desire to pursue drug addiction treatment as a “rescue indication.” If development for the initial indication was not halted due to unacceptable toxicities or insurmountable pharmacokinetic problems, such a collaborative development project can represent an attractive opportunity for NIDA. While the first step in such a collaboration may be to evaluate the compound in animal models of addiction, promising findings may not be essential if the compound has a unique mechanism of action and a strong theoretical rationale for efficacy.

**Avoiding False Positives in Drug Self-administration and Relapse Model Testing**

When administered as a pretreatment to animals trained to obtain a reinforcer by operant responding (e.g., lever-pressing by a rat, nose-poking by a mouse, or key-pecking by a pigeon), high doses of virtually any central nervous system (CNS)-active drug will decrease responding for the reinforcer. This is true regardless of the nature of the
reinforcer (whether it be the delivery of a food pellet or an intravenous infusion of a rewarding drug) and it stems from the ability of CNS-active drugs to cause sedation or ataxia, or to stimulate interfering behaviors, such as stereotypic grooming. For the purpose of the present discussion, this phenomenon will be referred to as a “general suppression of responding.” The challenge to those who use the drug self-administration technique in evaluating potential addiction treatment medications is clear: how can favorable findings (e.g., the ability of a pretreatment medication to modify the rewarding effects of a self-administered drug) be differentiated from a general suppression of responding?

The most common approach to ruling out a general suppression of responding is to demonstrate that a potential medication decreases responding for a drug of abuse but does not suppress responding for an alternative reinforcer, such as food. For example, doses of varenicline that decrease nicotine self-administration in rats have been shown to lack effects on responding for food.17 Likewise, doses of buprenorphine that decrease opiate self-administration in monkeys have been shown to lack effects on responding for food.15 Many false positives can be avoided if the demonstration of such selectivity is regarded as a positive result and the absence of such selectivity is regarded as a negative result. It must be acknowledged, however, that false negatives will follow from such a rigid definition of a positive result. For example, using the same procedure that demonstrated a positive result for buprenorphine, Mello et al.15 found that methadone caused a non-selective (general) suppression of responding for intravenous opiates. If one keeps in mind that medication screening is not hypothesis testing, but rather a probability endeavor to maximize the likelihood of success given limited resources, such false negatives are acceptable.

In medications discovery, we sometimes experience a conflict between our desire to achieve a low percentage of false positives (which can waste valuable drug development resources) and our desire “not to miss anything” and avoid false negatives from animal models. If we act on the former desire, we strive to achieve a high positive predictive value (defined as the number of true positives divided by the sum of all true and false positives) and if we act on the latter desire, we strive to achieve a high sensitivity (defined as the number of true positives divided by the sum of all true positives and false negatives). In general, researchers within pharmaceutical companies must acknowledge the high costs of drug development and, therefore, they strive to avoid false positives and achieve a high positive predictive value. False negatives are regarded as a necessary evil.iii In contrast, most researchers in academia are detached from the costs of drug development and they are more accustomed to hypothesis testing than medication screening. For both of these reasons, researchers in academia may be less accepting of false negatives. Perhaps this is why we often see no attempt to rule out a general suppression of responding in published findings from drug self-administration studies. Although this non-critical use of the drug self-administration technique in medications discovery may achieve high sensitivity, the value of this strategy is highly

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iii Please refer to Markou et al., Contribution of animal models and preclinical human studies to medication: Development for nicotine dependence, for further discussion of the consequences of false negative results in drug discovery.
questionable given the likelihood that most compounds with CNS activity will appear as positives.

The challenge of differentiating desirable findings from a general suppression of responding is also relevant to studies that use the increasingly popular models of relapse to drug self-administration behavior. In these models, animals are trained to self-administer a drug of abuse, their level of responding is then reduced by exposure to repeated extinction sessions in which saline is substituted for the drug of abuse, and their response rates are finally assessed after exposure to “relapse triggers” such as footshock, conditioned cues, or a priming dose of the previously self-administered drug. The relapse triggers stimulate responding (drug seeking behavior) even though the drug of abuse is no longer available. In test sessions, potential medications are evaluated for efficacy in blocking the ability of the relapse triggers to simulate responding. Unfortunately, rates of responding during relapse model test sessions (like the standard drug self-administration test sessions discussed above) can be decreased by sedative drug effects or by the stimulation of interfering behaviors.

One need to only examine some of the most recently published studies using relapse models to find cases in which investigators have touted the ability of test compounds to block relapse trigger-induced responding without attempting to rule out a general suppression of responding. Such studies often include data that show the test compound has no effect on rates of responding measured on an inactive lever (one with no programmed consequences for pressing) present within the operant chamber. While it may be tempting to conclude that adequate selectivity has been demonstrated if responding on the drug-associated lever is significantly decreased while responding on an inactive lever is not, this approach is inappropriate for at least two reasons. First, the rate of responding on the inactive lever is much lower than the rate of responding on the formerly drug-associated lever. Because test compounds can produce rate-dependent effects, both increasing low rates of operant responding and decreasing high rates of operant responding at a given test compound dose, it is critically important that, in the absence of test compound, response rates for the selectivity control be at least as high as response rates on the formerly drug-associated lever. Second, it is conceivable that the few “responses” occurring on the inactive lever may represent unintentional pumping of the lever while the animal is grooming or ambulating in the chamber. Such unintentional responses could be unaltered even if intentional lever-pressing is decreased through a general suppression of responding.

In fact, if a test compound were to stimulate locomotor activity in the chamber, accidental bumping of the inactive lever could increase while intentional responding on the formerly drug-associated lever could be suppressed by the interfering behavior.

Perhaps the best approach to ruling out a general suppression of responding in relapse model studies is to compare data from different relapse models. For example, in a NIDA contract study using cocaine relapse models, the kappa-opioid receptor antagonist JDTic was shown to block footshock-induced responding completely at a dose that did not suppress cocaine-primed responding. Alternatively, some investigators have taken the approach of comparing data from relapse model studies with data from drug or food self-administration studies; in such cases, investigators claim that a general suppression of responding has been ruled out if a test compound reduces responding during relapse model test sessions but does not directly affect responding.
for drug or food. This approach appears questionable because drug or food self-administration studies always involve the delivery of a reinforcer according to a schedule that differs from the “no reinforcem" schedule that is in effect during relapse model test sessions. In operant studies, a given drug can decrease rates of responding when one schedule of reinforcement is used and increase rates of responding when a different schedule of reinforcement is used. Thus, in ruling out a general suppression of responding, it can be argued that data from relapse model studies should only be compared with data from other studies that assess test compound effects on non-reinforced responding. In this vein, studies of test compound effects on responding during extinction sessions (following either food or drug self-administration training) could serve as appropriate controls.

TRANSLATIONAL RESEARCH, HUMAN LABORATORY MODELS, AND THE BRIDGE BETWEEN ANIMAL MODELS AND CLINICAL EFFICACY TRIALS

Translational research, involving the combined talents and knowledge of clinical and preclinical researchers, offers the hope of achieving greater success in clinical trials through the development of preliminary efficacy data or "proof of principle" on a compound prior to testing in a full-scale clinical trial. In fact, for quite a few years, NIDA has gathered subjective effects data as an important part of Phase IB safety interaction studies required by the FDA. In these Phase IB studies, subjects with experience with drugs of abuse are exposed to both the investigational medication and cocaine to insure that test compounds do not exacerbate the cardiovascular effects of cocaine, or affect its pharmacokinetics, given that in Phase II efficacy trials, subjects are likely to use cocaine. In these trials subjects have routinely been asked to rate the subjective effects (euphoria, anxiety, etc.) produced by the treatment drug alone as well as cocaine in the presence and absence of the potential medication in order to gain some preliminary understanding of a compound's ability to modify cocaine seeking and cocaine effects. It is not clear whether this form of "translation" has been helpful because no compound has been clearly successful in a Phase II trial.

For drug development in general, the success rate for new drug molecules in entering Phase II across indications has been low; estimated to be one in five for last few years. In medication development for cocaine abuse disorders, only a handful of new drug molecules have been developed, and few have progressed beyond Phase I for reasons of safety. One exception, ecopipam, originally evaluated as an antipsychotic, is discussed below. This difference from industry experience is attributable to the relatively small number of organizations that are both capable of, and interested in advancing new molecules from preclinical efficacy studies to safety studies necessary for filing an IND for drug abuse indications. Instead, as a result of the urgent need to evaluate

\[19\] Please refer to McEvoy and Freudenreich, Issues in the design and conductance of clinical trials in Volume 1, Psychiatric Disorders for further description of clinical trials of candidate drugs for the treatment of behavioral disorders, and changes undergoing in clinical trial design.
compounds in clinical trials for drug abuse, many compounds that are marketed for other indications and for which a case can be made for potential clinical efficacy based on mechanism of action have been studied in small clinical trials. Because of the involvement of dopaminergic mechanisms in drug abuse and the ubiquity of the dopamine system throughout the brain, a convincing rationale can be developed for compounds with mechanisms of action that modulate or impinge on the dopaminergic circuitry, and as a result, compounds with clinical status as anticonvulsants, antidepressants, antipsychotics, and anxiolytics have been evaluated in clinical trials for cocaine dependence. Often, these compounds have been advanced to clinical trials in the absence of any relevant animal data from preclinical models of drug abuse. As a result, many Phase II failures cannot be taken to reflect a problem in the validity of animal models of addiction. These failures often occur when compounds showing initial efficacy in small laboratory studies, single-site, or open label trials conducted by academic researchers fail to show efficacy in larger, double-blind and multi-site trials. This is in contrast to the industry model, in which most compounds fail in clinical trials after showing positive results in animal models. So the question of Phase II failure after achieving positive results in animal models can, at least in the field of drug abuse, be broadened to include Phase II failures after achievement of positive results in early human trials.

Human laboratory studies hold great promise as “translational” or “bridging” studies to determine, in the case of drug abuse research (1) whether effects seen in animal models will occur in humans and (2) how to evaluate drugs optimally in humans, both in terms of clinical dosing and study design. The challenge in this area of drug development is whether human laboratory studies can be designed to ask the “right” questions to insure clinical success and reduce late phase clinical failures.24 In the development of cocaine addiction treatments, it is not clear that there is a consensus on what the “right” questions might be: craving, self-administration, side effects, etc. The predictive value of both animal paradigms and human laboratory procedures is severely hampered by the absence of even one effective medication with which to validate the models. There are a number of human clinical laboratory designs that have been developed, many of which were designed to measure abuse liability, but increasingly, human laboratory models are aimed at evaluation of potential treatment medications. These designs typically use rating and visual analog scales to measure craving, subjective effects, perceived value of cocaine, as well as physiological interactions with cocaine on cardiovascular and pharmacokinetic measures.9 One design that has been used extensively is human laboratory cocaine self-administration, in which subjects sample various doses of cocaine in the presence of a medication, and subsequently make choices to either self-administer the available dose of cocaine or obtain a monetary voucher.25 Other models have measured craving or wanting following stress, exposure to cues,26 or withdrawal effects of cocaine, all of which seem to be important endpoints that theoretically should predict clinical success. Although both animal and human laboratory models predicted the success of buprenorphine for

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9 Please refer to Rocha et al., Development of medications for heroin and cocaine addiction and regulatory aspects of abuse liability testing in this volume for further discussion regarding translational initiatives in substance abuse treatment and abuse liability potential.
opiate-dependence treatment (e.g., \textsuperscript{27,28}), and it can be used to validate models for opiate treatment, the lack of even one effective (FDA-approved) medication for cocaine dependence means that there have been many false positive predictions of efficacy using these models, but not a single true positive.

So have our animal models in cocaine treatment research failed us, as some have suggested? There are very few examples of compounds that failed Phase II efficacy studies despite positive animal models. Two that can be found will be described for illustrative purposes, but unfortunately, the results of both Phase II clinical trials are not published at the time of this writing, so the details and possible “reasons” for failure are not available for careful analysis and discussion. The compounds are ecopipam, a dopamine D\textsubscript{1} receptor antagonist, and baclofen, a GABA\textsubscript{B} receptor agonist.

Ecopipam is a dopamine D\textsubscript{1}/D\textsubscript{5} receptor antagonist that was developed by Schering-Plough as an antipsychotic. There was a wealth of published data from animal models in which D\textsubscript{1} ligands have been implicated in the behavioral effects of cocaine. Early self-administration studies in which D\textsubscript{1} receptor antagonists were administered prior to a single dose of cocaine produced robust increases in responding, confirming the importance of these receptors in the reinforcing effects of cocaine.\textsuperscript{29,30} When ecopipam was administered as a pretreatment in primate studies using the entire dose–effect curve for cocaine self-administration and other behavioral effects, it was found to produce rightward shifts in the cocaine dose–effect curve.\textsuperscript{31,32} It should be noted that both of these early studies observed that the antagonism was surmountable and not irreversible, which was consistent with the earlier studies in rodents.

Human laboratory studies were conducted that indicated that single acute doses of ecopipam (10, 25, and 100 mg) decreased both the desire to take cocaine, and the stimulating effects of a 30 mg/kg infusion of cocaine. In addition, the euphoric and anxiogenic effects of cocaine were reported to be attenuated.\textsuperscript{33} A later laboratory study that used a chronic dosing paradigm (100 mg for 5 days) indicated that smoked cocaine self-administration was increased, as were its subjective effects,\textsuperscript{34} and another laboratory study reported that ecopipam (10, 25, and 100 mg) failed to alter the subjective effects of intravenous cocaine and potentiated the cardiovascular response to cocaine.\textsuperscript{35}

Unfortunately, the results of the multi-site outpatient clinical trial were never published, but it is widely known that the trial was terminated prematurely because an interim data analysis suggested a lack of efficacy. Could its failure have been more accurately predicted by both animal and human laboratory models? Hindsight is 20/20, so a retrospective analysis can point to the slight rightward shifts in cocaine self-administration in animal models that might have predicted that subjects would simply take additional drug to counteract the medication. Similarly, it has been known for years that chronic doses of dopamine receptor antagonists produce increased receptor sensitivity. This may explain both the potentiated cocaine reinforcement following chronic administration in the human laboratory and the negative Phase II outcome. There are a number of possible issues in the interpretation of both human and animal laboratory studies.\textsuperscript{36}

Another example that yields no simple answers as to the predictive validity of animal models is the study of baclofen, a GABA\textsubscript{B} receptor agonist and clinically available drug used as an antispasmodic and muscle relaxant. This compound was the subject of so many investigations of its effects against cocaine and other drugs of abuse that entire review articles have been written to describe them.\textsuperscript{37,38} In general, using a number
of different experimental paradigms, baclofen has been widely reported to reduce the self-administration of cocaine in animals using progressive ratio schedules, second-order and fixed ratio schedules with little effect on food-reinforced behavior.

In a human laboratory study that preceded the clinical trial, patients were maintained on baclofen (0, 30, or 60 mg PO) for a period of 7 days. At days 3–4 and 6–7, each volunteer was challenged with smoked cocaine (0, 12, 25, and 50 mg), with subjects subsequently asked to choose to self-administer the available dose of cocaine or to receive a voucher. Baclofen at a dose of 60 mg was found to decrease self-administration of the low (12 mg) dose of cocaine. At 30 mg baclofen, the perceived value of 50 mg cocaine was also decreased.

When baclofen was studied in clinical pilot study of 70 subjects, it was reported that baclofen (20 mg t.i.d. or placebo) for 16 weeks resulted in statistically significant reductions in cocaine use as compared to placebo as indicated by urine benzoylecgonine levels. The effect was most pronounced for subjects with higher levels of cocaine use at baseline, and was used to justify a full-scale multi-site study. Like with ecopipam, the results of the multi-site study have not yet been published although a manuscript is in preparation and may be published soon. Baclofen did not demonstrate efficacy greater than placebo, but the reasons for its lack of efficacy are not completely clear and may be related to the subject population, side effects, or other factors yet to be determined. Whether these results could have been predicted by either animal models or human laboratory studies will be facilitated by the disclosure of the results through publication, which will permit the “bedside-to-bench” feedback that is so urgently needed. So for both ecopipam and baclofen, animal models suggested decreases in cocaine self-administration, a seemingly positive outcome for a potential treatment medication. In both cases, at least some of the human laboratory studies were consistent with animal models, but did not predict the negative Phase II clinical outcome. For ecopipam, two of the three human laboratory studies were negative, but the relationships of the effects reported in those studies to the reasons for trial failure are also unknown. The question of whether it would have been theoretically possible to predict the Phase II clinical failure if the “right” questions had been asked of the laboratory studies or if the trial had been designed differently, perhaps as a relapse prevention trial, is simply not known at this time, although the results of the baclofen trial, when published, may be illustrative. Thus the Phase II failure rate for drug abuse medications does not appear to be the sole result of failure of animal models to predict clinical outcomes accurately. Studies using translational models to extend the animal model data to ask the kinds of questions that would have predicted Phase II failure may not have occurred. So the question of whether the failure rate of clinical trials could be reduced by the judicious use of translational human laboratory studies and small efficacy trials remains to be addressed.

Our perspective is that Phase II clinical trial failures for stimulant dependence stem mainly from our inability to validate any of our animal or human laboratory models with a positive control, meaning an effective medication. The complexity of the disorder, with interactions among genetics, environment, and behavior, as well as the heterogeneity of the populations available for study, may make a successful Phase II outcome in a multi-site clinical trial a particularly difficult challenge. Human laboratory techniques have been developed to predict clinical efficacy, but like the animal models,
they appear to have resulted in false positives in at least a few cases. Whether we can design human laboratory studies that will unveil the issues predictive of a successful Phase II trial remains to be determined.

Overall, there have been remarkable successes in the development of medications for opiate addiction, and there are significant challenges ahead for development of medications for stimulant dependence. NIDA has developed a highly effective infrastructure for the evaluation of the efficacy and safety of potential medications through the DPMC and its associated grantees and contractors. Animal models in the field of drug abuse are some of the best behavioral paradigms available for any CNS disorder, and drug abuse researchers have pioneered the use of translational human laboratory studies to guide Phase II evaluations. Although stimulant abuse disorders are complex and challenging, it is anticipated that these resources will ultimately lead to success.

REFERENCES


